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Heart rate variability and heart rate asymmetry in adolescents with major depressive disorder during nocturnal sleep period

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Abstract

Background Although reduced heart rate variability (HRV) has been observed in adolescents with major depressive disorder (MDD), substantial between-study heterogeneity and conflicting outcomes exist. Moreover, few studies have investigated heart rate asymmetry (HRA) features despite the high sensitivity of nonlinear indices to heart rate fluctuations. This study aimed to investigate the variations in HRV measures, especially the nonlinear features of HRA, among adolescents with MDD during the nocturnal sleep period.

Methods Adolescents with MDD and healthy controls completed the clinical assessment of depressive symptom severity and sleep quality followed by a three-night sleep electrocardiogram (ECG) monitoring. Traditional time-domain and frequency-domain HRV measures, nonlinear HRA measures, and the prevalence of different HRA forms and HRA compensation were calculated.

Results A total of 61 participants with 154 nocturnal ECG time series were available for analysis. Vagally-mediated HRV measures, such as RMSSD, PNN50, and HF, as well as $C1_d$ were statistically lower in clinically depressed adolescents compared with healthy controls, whereas $C2_d$ was significantly higher. A substantial decrease in the prevalence of short-term HRA, long-term HRA, and the corresponding compensation effect were also observed. In contrast to the medium to large effect sizes observed in traditional HRV indices, nonlinear HRA features showed extremely large effect sizes in discriminating MDD ($C1_d$: Cohen's $d = -1.38$; $C2_d$: Cohen's $d = 1.11$), and exhibited a statistical correlation with the severity of depression ($C1_d$: rho $= -0.269$; $C2_d$: rho $= 0.243$). Moreover, there were no significant differences in the distributions of nocturnal HRA measures collected over various nights.

Conclusion Adolescents with MDD suffered a significant decrease in vagal tone compared to healthy controls, and the features focusing on the directionality of heart rate variations may provide further information on cardiac autonomic activity associated with depression.

Keywords Major depressive disorder, Heart rate variability, Heart rate asymmetry, Biomarker, Adolescents

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Introduction

Adolescence is the lifetime peak period for the onset of major depressive disorder (MDD), with an increasing 12-month prevalence of 4–20% worldwide [1, 2]. The burden of depression is considerable since it is associated with impaired school performance, interpersonal difficulties later in life, increased risk of other mental or somatic disorders, and high suicide risk [3–6]. Over one-third of adolescent-onset depression had recurrence above 18 years of age [7]. However, MDD is often underdiagnosed with only 50% of adolescents diagnosed before reaching adulthood [8]. Adolescence represents a vulnerable age period to a probable depression-induced neuro-dysregulation and cardiac autonomic dysfunction [9–11]. Considering the current diagnosis of MDD is primarily dependent on the subjective assessments of clinicians, introducing an appropriate and objective diagnostic marker is critical for early detection and timely treatment.

MDD has been suggested as an independent risk factor for the onset and progression of cardiovascular diseases [12]. The autonomic nervous system plays a major role in the regulation of cardiovascular function [13], and one plausible mechanism for the correlation between MDD and cardiovascular diseases is autonomic dysfunction. Heart rate variability (HRV), a particularly sensitive measure of autonomic activity, characterizes the variations in heartbeats and reflects the dynamic interaction and balance between acceleratory sympathetic nervous system and decelerator parasympathetic nervous system [14]. HRV measurements have time and cost advantages while also being noninvasive and easily applicable. Consequently, HRV has been widely studied to reveal links between mental processes and cardiac autonomic regulation [15].

The methods for HRV analysis can be roughly divided into two categories, including the measures considering the magnitude of variations in beat-to-beat RR intervals and the measures taking into account the directionality of the variations (shortening or prolongation of RR intervals). The former approaches range from simple time-domain methods, such as the standard deviation of RR intervals (SDNN) and the root mean square of successive differences (RMSSD), to frequency-domain methods, such as the high-frequency power component (HF, 0.15–0.4 Hz) and the low-frequency power component (LF, 0.04–0.15 Hz) yielded by analyzing the Fourier spectrum, and to the complexity like symbolic dynamics index [16–18]. As suggested by a recent meta-analysis on MDD in adolescents [19], a considerably reduced vagal activity has been identified using HRV measures, but substantial between-study heterogeneity and conflicting outcomes exist as well. Measures with large effect sizes, such as HF and RMSSD, have shown high levels of heterogeneity, whereas the inconsistent directions of changes in the features such as SDNN and LF have been attained across studies [15, 17, 20]. Meanwhile, most studies have focused on short-term resting state HRV lasting for 5 min. Given the instability and unpredictability of short-term data, the researchers using long-term recordings are demanded to verify the reliability and validity of existing results.

Approaches to heart rate asymmetry (HRA), aiming to separately explore the behavior of decelerations and accelerations of heart rhythm, have been attracting increasing attention. The potential mechanisms involved in HRA include respiratory patterns and various physiological reflexes, such as the baroreflex regulating the cardiovascular system [21, 22]. A significant reduction in HRA features has been observed in subjects with attention-deficit/hyperactivity disorder, heart failure, vasovagal syndrome, gastric cancer, or a history of diabetes [23–26], but the influence of MDD on HRA features in adolescents has only been examined in one study [27]. Additionally, a compensatory phenomenon has been demonstrated in HRA analysis, that in healthy subjects, the contributions of heart rate decelerations are greater than those of accelerations for short-term HRV, whereas the contributions of accelerations are greater than those of decelerations for long-term HRV [28, 29]. However, no studies related to HRA compensation have been performed in adolescent major depression. In view of the high sensitivity of nonlinear indices to heart rate fluctuations in adults with MDD, the performance of HRA-related measures is promising [30]. Moreover, additional research on the correlation between depression severity and measures is required to confirm the utility of autonomous regulation of the heart rate as a possible biomarker, due to the unsatisfactory outcomes of traditional HRV measures [15, 31, 32].

In consideration of the strong link between sleep and depression [33] and the good long-term stability of sleep data not being affected by temporary emotional states, nocturnal electrocardiogram (ECG) signal was chosen as the target data for this study. We hypothesize that in adolescents with MDD, reduced HRV can be consistently identified in long-term nocturnal ECG recordings, and the expression of HRA differs from that of healthy controls with a close connection to depression severity and without altering over time. Accordingly, the objectives of this study were to investigate the following: (i) variations in traditional HRV measures derived from time domain and frequency domain, nonlinear indices of HRA, and the prevalence of HRA phenomena among clinically depressed adolescents; (ii) associations between measures and depressive symptom severity. Furthermore, the consistency of findings in HRV and HRA measures collected over various nights was analyzed.

Methods

Participants

We recruited 28 adolescent patients (13 male, average age: 15.8 ± 1.9 years) with unipolar depressive disorder from the inpatients admitted to the Affiliated Mental Health Center, Zhejiang University School of Medicine, and 33 age-matched healthy subjects (14 male, average age: 15.4 ± 0.5 years) from a high school.

The diagnosis of MDD was classified by thorough clinical investigation based on a structured diagnostic interview by a certified psychiatrist according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [34]. The exclusion criteria for both MDD and control groups were the following: (1) obesity with a body mass index (BMI) over 30; (2) a history of cardiovascular, respiratory, neurological, or metabolic diseases; (3) mental retardation, substance dependence or abuse, bipolar disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and eating disorder defined by DSM-5; (4) presence of psychotic symptoms or suicidal tendencies. The control participants as well as their first-degree relatives had never been treated for any mental disorders. This study was approved by Hangzhou Seventh People's Hospital Ethics Committee (No. 2024033). All participants and their parents were carefully informed about the study protocol and written informed consent was obtained prior to the examination.

Clinical measures

Trained clinical raters with appropriate inter-rater reliability (Spearman's rho = 0.83) conducted a semi-structured interview with all adolescent participants [35] and completed the Hamilton Depression Rating Scale (HDRS-17) to determine the severity of depressive symptoms [36]. Participants also completed a self-administrated sleep assessment using the Pittsburgh Sleep Quality Index (PSQI) [37], which estimated total sleep time, sleep quality, sleep medication use, sleep disturbance, daytime dysfunction, sleep latency, and symptoms affecting sleep over the last month. These clinical assessments took place before the measurements of ECG signals.

Sleep ECG recordings and preprocessing

A three-night sleep ECG monitoring in the ward or at home was taken for each participant. Participants were instructed not to smoke or take caffeine-containing soft drinks for at least 12 h before the examination. Data collection was performed overnight in the supine position using CP-025 (Beneware, Hangzhou, China), a single-lead wearable ECG recorder with a sampling rate of 200 Hz. The participants received written guidelines for using the devices.

The raw data of nocturnal ECG were transferred offline to a PC for data storage, on-screen monitoring, and preliminary automatic identification of R-peaks with the use of HolterSystem software (Beneware, Hangzhou, China). Necessary corrections of misidentified R-peaks caused by artifacts and supplements of missing R-peaks were manually operated following a visual inspection of all ECG signals, with the assistance of tools provided by the software. As a result of the significant differences in sleep durations among participants with a median recording period of 7.7 h (IQR 7.3–9.2 h), a specific and continuous ECG recording, which starts at least 2 h after recording and lasts for 4 h, was selected for each night and the corresponding RR sequences were extracted for further HRV analysis using Python (Python Foundation, USA). The overnight recordings with large data loss or without continuous 4-h data were excluded from the analysis.

Heart rate variability analysis

Nocturnal RR recordings were analyzed using traditional HRV measures derived from the time domain and frequency domain, as well as nonlinear indices of HRA.

Traditional time domain and frequency domain analysis

Concerning the time domain analysis, the mean value of RR intervals (RR mean, ms), SDNN (ms), RMSSD (ms), and the percentage of the number of successive heartbeats differing > 50 ms (PNN50) (%) were evaluated.

Concerning the frequency domain analysis, the time series of RR intervals were resampled using cubic spline interpolation with the frequency of 4 Hz, and features of HF, LF, total power (TP), as well as the ratio of LF to HF (LF/HF) were consequently obtained using spectral analysis of fast Fourier transform.

Considering that short RR recordings of a 5-minute duration can be advantageous to examine autonomic modulation for traditional HRV measures with relatively clear physiological implications [38], the 4-hour long RR intervals of each night were divided into consecutive 5-minute segments without overlapping. Each night's profile of RR intervals and HRV measures were determined by averaging the individual values of all these segments [39].

Heart rate asymmetry analysis

The Poincaré plot of RR intervals, a scatter plot of the current RR interval plotted against the preceding RR interval, was applied to describe HRA illustrating the behavior of decelerations and accelerations of heart rhythm. Short-term and long-term HRAs of the 4-hour RR intervals were quantified using the contributions of heart rate decelerations to short-term and long-term HRVs described by $C1_d$ and $C2_d$ [28, 40], respectively. $C1_d$ and $C2_d$ were defined as follows:

Table 1 Demographic characteristics of the MDD and control groups

	MDD group ($n=28$)	Control group ($n=33$)	Cohen's d (95% CI)	*P*-value
Nocturnal RR intervals time series	78	76		
Sex (female/male)	15/13	19/14		0.800
Age (years)	15.79 ± 1.93	15.39 ± 0.50	0.29 (–0.21 ~ 0.80)	0.106
Height (cm)	165.43 ± 9.15	168.15 ± 9.53	–0.29 (–0.80 ~ 0.22)	0.345
Weight (kg)	56.16 ± 12.67	54.60 ± 11.83	0.13 (–0.38 ~ 0.63)	0.667
BMI (kg/m^2)	20.35 ± 3.35	19.12 ± 2.62	0.41 (–0.10 ~ 0.92)	0.151
HDRS	24.57 ± 5.32	3.94 ± 3.80	4.53 (3.58 ~ 5.47)	**< 0.001**
PSQI	11.00 ± 3.97	4.46 ± 3.11	1.85 (1.25 ~ 2.45)	**< 0.001**

MDD, major depressive disorder; CI, confidence intervals; BMI, body mass index; HDRS, Hamilton Depression Rating Scale; PSQI, the Pittsburgh Sleep Quality Index. Data are expressed as mean ± standard deviation

Table 2 Comparison between the patient group and control group

	MDD group ($n=78$)	Control group ($n=76$)	Cohen's d (95% CI)	*P*-value
RR mean (ms)	912.552 ± 115.765	928.028 ± 123.060	–0.13 (–0.45 ~ 0.19)	0.311
SDNN (ms)	58.664 ± 35.492	62.661 ± 30.993	–0.12 (–0.44 ~ 0.20)	0.286
RMSSD (ms)	50.439 ± 36.767	56.001 ± 28.405	–0.17 (–0.49 ~ 0.15)	**0.023**
PNN50 (%)	12.065 ± 10.333	17.815 ± 8.878	–0.60 (–0.92 ~ –0.27)	**< 0.001**
HF (log)	5.015 ± 0.432	5.281 ± 0.335	–0.69 (–1.01 ~ –0.36)	**< 0.001**
LF (log)	4.385 ± 0.389	4.589 ± 0.236	–0.63 (–0.96 ~ –0.31)	**< 0.001**
TP (log)	5.198 ± 0.385	5.439 ± 0.279	-0.72 (-1.04 ~ -0.39)	**< 0.001**
LF/HF	0.876 ± 0.053	0.871 ± 0.043	0.10 (–0.21 ~ 0.42)	0.640
$C1_d$	0.487 ± 0.026	0.521 ± 0.023	–1.38 (–1.74 ~ -1.03)	**< 0.001**
$C2_d$	0.494 ± 0.018	0.476 ± 0.014	1.11 (0.77 ~ 1.45)	**< 0.001**

MDD, major depressive disorder; CI, confidence intervals; RR mean, the mean value of RR intervals; SDNN, standard deviation of RR intervals; RMSSD, root mean square of successive differences; PNN50, percentage of the number of successive heartbeats differing > 50 ms; HF, high frequency power; LF, low frequency power; TP, total power; LF/HF, ratio of low frequency to high frequency; $C1_d$, contributions of heart rate decelerations to short-term heart rate variability; $C2_d$, contributions of heart rate decelerations to long-term heart rate variability. Data are presented as mean ± standard deviation

$$C1_d = SD1_d{}^2/SD1^2 \text{ and } C2_d = SD2_d{}^2/SD2^2,$$

$SD1^2$ and $SD2^2$ represent the variance of the dispersion of points in the Poincaré plot of RR intervals across the identity line and along the identity line, respectively, whereas $SDi_d{}^2$ (i = 1, 2) represents the part of SDi^2 (i = 1, 2) related to heart rate decelerations.

The phenomenon of short-term HRA is present when $C1_d > 0.5$, and long-term HRA exists when $C2_d < 0.5$. Heart rate asymmetry compensation occurs when both conditions are satisfied, that is, $C1_d > 0.5$ and $C2_d < 0.5$.

Statistical analysis

The group differences between participants with and without MDD were compared using the Mann-Whitney U test in consideration of their non-normal distribution. Specially, the differences in the prevalence of different HRA forms, HRA compensation, and sex between the two groups were examined with Fisher's exact test. Correlation analysis was subsequently employed to investigate the associations between measures and depression severity measured by HDRS scores, using Spearman's rank correlation test. Besides, the Wilcoxon signed-rank test was also implemented to contrast the distributions of nocturnal HRV measures collected over various nights to examine the stability of measures.

The effect sizes between the MDD and the control group were calculated by Cohen's *d*. Effect sizes of 0.2, 0.5, and 0.8 were categorized as having minimal, moderate, and substantial effects, respectively [41]. All statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, USA) and STATA 17.0 (StataCorp, Texas, USA). All tests were two-tailed with statistical significance defined as $P < 0.05$.

Results

Group characteristics

A total of 61 participants with 154 nocturnal RR intervals time series were available for analysis in the study. Patients with MDD and healthy controls did not differ in sex, age, weight, height, or BMI. The patient group showed moderate to severe depression (mean HDRS score = 24.57) and poor sleep quality (mean PSQI score = 11.00). Group characteristics are provided in Table 1.

Between-group comparison of HRV/HRA measures

Between-group tests on measures of heart rate and automatic nervous system activity are summarized in Table 2. HRV measures (RMSSD, PNN50, HF, LF, TP) and $C1_d$ were statistically lower in clinically depressed adolescents compared with healthy controls, whereas $C2_d$ was

significantly higher. $C1_d$ yielded the largest effect size (Cohen's $d = -1.38$), followed by $C2_d$, TP, HF, LF, PNN50, and RMSSD with effect sizes of 1.11, −0.72, −0.69, −0.63, −0.60, and −0.17, respectively. No significant differences were observed between the MDD group and control group in terms of mean RR interval, SDNN, and LF/HF.

Prevalence of HRA phenomena

The prevalence of different HRA forms and HRA compensation for the two groups is presented in Fig. 1. In adolescents with MDD, short-term asymmetry was revealed in 29.5% of recordings (23/78), long-term asymmetry in 64.1% (50/78), and both types of HRA coexisted in 28.2% (22/78). The control group had significantly higher prevalence rates: 85.5% for short-term asymmetry (65/76 recordings, $P < 0.001$), 94.7% for long-term asymmetry (72/76 recordings, $P < 0.001$), and 85.5% for HRA compensation (65/76 recordings, $P < 0.001$). All recordings from healthy participants with short-term asymmetry also exhibited HRA compensation. Figure 2 shows two typical Poincaré plots of RR intervals from clinically depressed and healthy participants. The distribution of RR intervals in healthy subjects was more dispersed than that in patients.

Correlation between HRV/HRA measures and depression severity

HRV measures of RMSSD, PNN50, HF, LF, and TP, and HRA measures of $C1_d$ and $C2_d$, which can differentiate patients from healthy adolescents, were further investigated concerning the relationship with depressive symptoms. Correlations using data from clinically depressed adolescents revealed a significant negative correlation of HDRS with RMSSD (rho = −0.255, $P = 0.024$), PNN50 (rho = −0.231, $P = 0.041$), HF (rho = −0.236, $P = 0.037$), TP (rho = −0.245, $P = 0.032$), and $C1_d$ (rho = −0.269, $P = 0.017$), and a positive correlation of HDRS scores with $C2_d$ (rho = 0.243, $P = 0.032$). However, no significant interaction was found between LF and depression severity.

Impact of data collection time

The distributions of nocturnal HRV and HRA measures collected over various nights were contrasted (Table 3). A total of 51 participants completed two nights of high-quality ECG recordings, and 40 subjects achieved three nights. The measures of mean RR intervals, HF, LF, and TP were highly variable and sensitive to the timing of data collection.

Discussion

In this study, autonomic activity in adolescents with MDD was evaluated using traditional HRV and nonlinear HRA analysis. Firstly, adolescents suffering from MDD showed a reduction in traditional time-domain and frequency-domain HRV measures using 4-hour nocturnal ECG recordings. Secondly, the phenomena of both short-term and long-term HRA in depressed adolescents as well as the corresponding compensation effect were significantly diminished. Thirdly, in contrast to the medium to large effect sizes yielded in traditional HRV indices, nonlinear HRA features revealed a strong ability to distinguish between MDD and healthy adolescents with extremely large effect sizes, showing statistical correlations with depression severity. Notably, HRA measures remained consistent across multiple nights of monitoring.

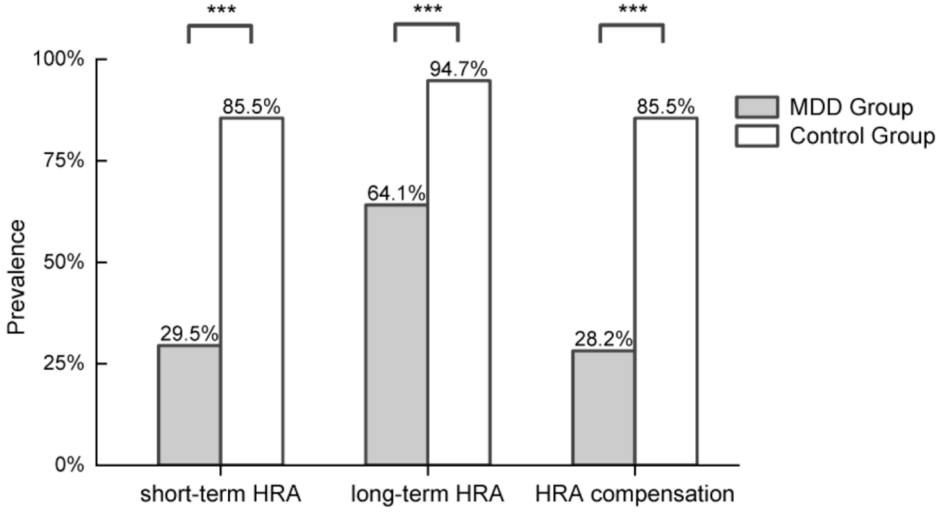

Fig. 1 Prevalence of different types of HRA and comparison between the patient ($n = 78$) and control ($n = 76$) groups. *** $P < 0.001$. HRA, heart rate asymmetry

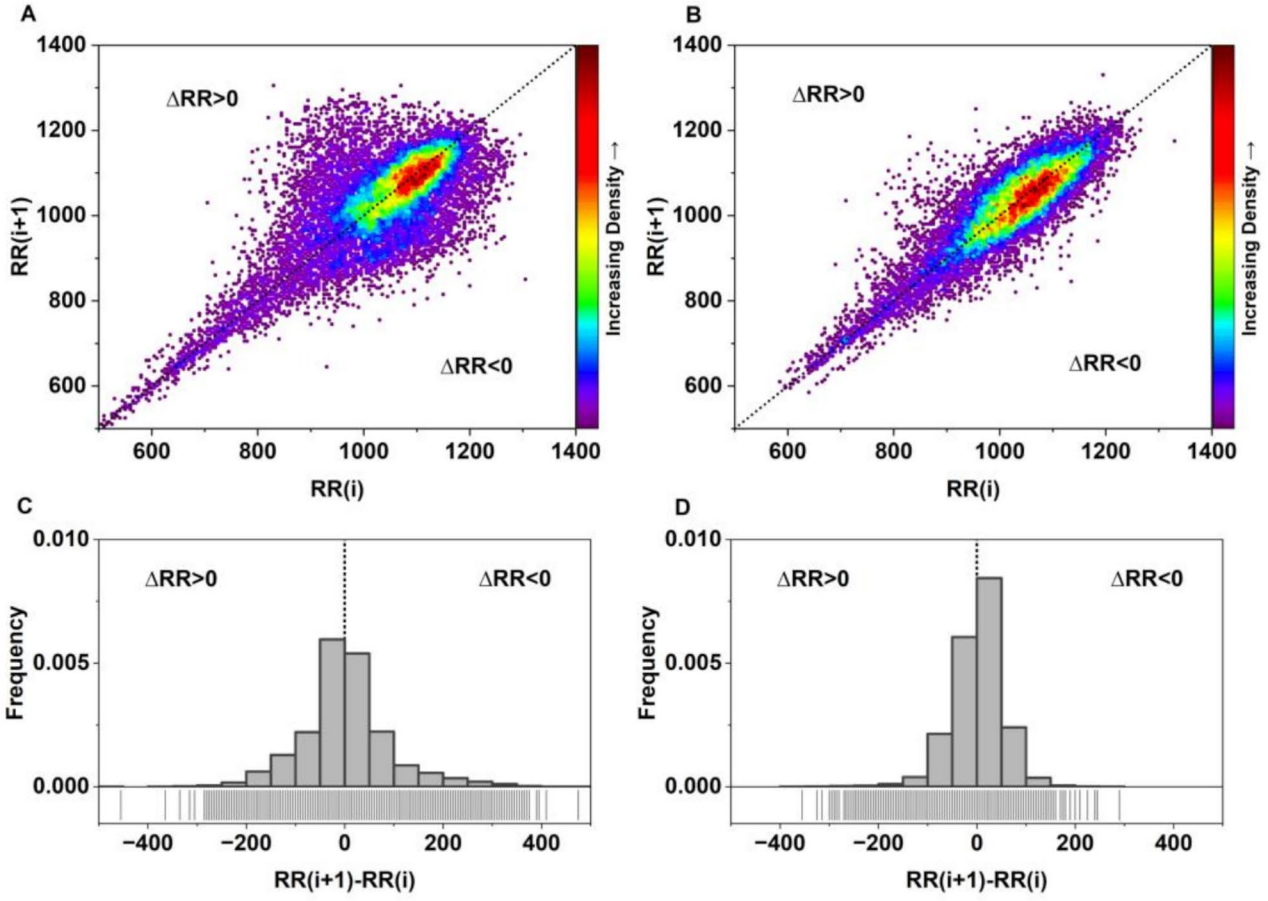

Fig. 2 Two typical Poincaré plots of RR intervals attained from healthy (left panel) and clinically depressed (right panel) participants with the scatter density plots in the plane (RR(i), RR(i + 1)) (**A** and **B**, respectively) and the corresponding distributions of ΔRR = RR(i + 1)– RR(i) (**C** and **D**, respectively)

Table 3 Comparison of the distributions of HRV and HRA measures collected over various nights

	Night1 & Night2 ($n=51$)	Night2 & Night3 ($n=40$)	Night1 & Night3 ($n=40$)
RR mean (ms)	**0.041**	0.361	0.289
SDNN (ms)	0.456	0.146	0.995
RMSSD (ms)	0.840	0.283	0.627
PNN50 (%)	0.629	0.554	0.265
HF (log)	0.391	**0.031**	0.092
LF (log)	0.818	**0.021**	0.232
TP (log)	0.386	**0.025**	0.115
LF/HF	0.225	0.211	0.146
$C1_d$	0.683	0.847	0.868
$C2_d$	0.527	0.444	0.162

RR mean, the mean value of RR intervals; SDNN, standard deviation of RR intervals; RMSSD, root mean square of successive differences; PNN50, percentage of the number of successive heartbeats differing > 50 ms; HF, high frequency power; LF, low frequency power; TP, total power; LF/HF, ratio of low frequency to high frequency; $C1_d$, contributions of heart rate decelerations to short-term heart rate variability; $C2_d$, contributions of heart rate decelerations to long-term heart rate variability. Data are *P* values of Wilcoxon signed-rank test

Comparison of HRV measures among clinically depressed adolescents

Instead of using single 5-minute RR intervals, the traditional HRV measures derived from time domain and frequency domain in this study were calculated using multiple consecutive 5-minute RR segments. Most findings aligned with previous studies employing short-term resting state ECG recordings. All vagally-mediated HRV measures including RMSSD, PNN50, and HF were statistically reduced and correlated with depression severity. There were no substantial associations found between MDD and LF. The recent meta-review showed no differences in LF with a high level of heterogeneity between clinically depressed and healthy adolescents [19], as well as the present study demonstrated little interaction between LF and depressive symptom severity. No alterations occurred in SDNN either, which are modulated by both sympathetic and parasympathetic activity and highly correlated with LF [16, 42]. Overall, this confirms the hypothesis proposed in the previous review that autonomic nervous system dysfunction in adolescents with MDD is predominantly driven by reduced vagal activity,

rather than increased sympathetic activity or joint sympathetic and parasympathetic functioning [19, 32].

The neurovisceral integration model and the polyvagal theory have supported the idea of linking the cardiac vagal control indexed by HRV and psychological processes [43, 44]. The former model connecting the heart to the prefrontal cortex assumes that the higher the vagal tone, the better executive cognitive performance, as well as better emotional and health regulation, whereas the latter based on the phylogeny of the neural circuits emphasizes the impact of vagal activity on social functioning. Accordingly, the decreased vagally-mediated HRV measures in this study were matched to the clinical manifestations of MDD in adolescents, including unstable peer and family relationships, poor school performance, and diminished emotion differentiation [45–48].

With regard to nonlinear HRA measures, a considerable decrease appeared in the contributions of heartbeat decelerations to short-term HRVs ($C1_d$) and an increase to long-term HRVs ($C2_d$) in adolescents with MDD. This implied that physiological processes make an effort to maintain a balance between short-term and long-term heart rate decelerations in response to depression, but insufficiently. Compared to the medium to large effect sizes observed in linear HRV measures, both $C1_d$ and $C2_d$ showed extremely large effect sizes in identifying depression from healthy controls with a significant connection to the severity of depression. The dynamic nonlinear indices regarding heart rate deceleration or acceleration capacities and patterns therefore may play a major role in the diagnosis and assessment of depression.

In addition, this study inspected the stability of HRV measures. Large variations with data collecting time were revealed in heart rate and spectrum features of LF, HF, and TP. This may indicate that time-domain HRV and nonlinear HRA features are more adept at capturing the depression-induced disturbances that exist in a stable manner in physiological signals, and longer lengths of RR intervals are demanded for frequency-domain features to minimize the influence of temporary autonomic nervous system activity. Interestingly, the instability of short-term HF may also contribute to the high level of between-study heterogeneity in meta-review since no trustworthy sources of heterogeneity were discovered [19]. Nevertheless, Vloet et al. [49] did not find any correlations between depression and HRV in adolescents using 24-hour ECG during everyday activity. In view of the fact that adolescents have higher cardiovascular autonomic reactivity than adults [50, 51], the data involving a relatively steady psychological and physiological state is recommended to avoid depression-related alterations being obscured by transient but intense autonomic activations.

Prevalence of HRA phenomena in clinically depressed adolescents

The prevalence of short-term and long-term asymmetry as well as its compensation were all statistically decreased in clinically depressed adolescents, with the decline in short-term asymmetry and HRA compensation being particularly notable. As discovered by Sibrecht et al. [52] and Zalas et al. [29], the prevalence of various HRA features exceeds 85% in healthy volunteers including children and adults. Depression-induced heavy loss in short-term asymmetry (56%) and HRA compensation (57.3%) offered important insights into the underlying physiological mechanism.

Although the real physiological origin is still uncertain, all factors regulating momentary heart rate may cause HRA, involving the factors naturally asymmetric such as the difference of delay in the sinus node's response to vagal tone changes and the sympathetic response, and the factors contributing to HRA such as hormones, cytokines, and emotional activity. From the perspective of cardiac autonomic regulation, some researchers have ascribed the decelerations-based part of variance and short-term HRA to the parasympathetic branch [28, 53], which was consistent with the findings in traditional HRV measures. Correspondingly, HRA compensation can be recognized as an effect of the antagonistic function of sympathetic and parasympathetic systems. However, the pathophysiological mechanism of depression-related alterations in HRA remains not fully understood. The evidence like the dysregulation of the hypothalamus-pituitary-adrenal axis, the depletion of brain serotonin, and the immune system response observed in depression might also be considered.

Limitations

Some limitations should be mentioned in this study. Firstly, several cardiovascular risk factors such as physical activity and inflammation were not carefully monitored. We just put limitations on smoking and caffeine-containing beverages before the data collection. Secondly, the lack of detailed labeling of sleep process, including wakefulness, sleep stages, and movement time makes it impossible to build a relationship among sleep, HRV, and depression. Thirdly, HRA measures were not thoroughly investigated. Although the scatter plots and the corresponding distributions of RR intervals showed a great difference between healthy and clinically depressed participants, only features of $C1_d$ and $C2_d$ and the related HRA phenomena were analyzed in this study. Furthermore, HRV analysis could benefit from methodological improvements, such as exploring algorithms like the Lomb-Scargle Periodogram, which could provide more accurate power spectral density estimation without the need for regular RR intervals or resampling.

Implications for future research

Regarding technical considerations, more novel asymmetry measures using variance-, symbol-, graph-based, and entropy approaches are needed to promote the accuracy of depression monitoring and advance our knowledge of cardiac nerve electrophysiology. Meanwhile, the application of machine learning algorithms using HRV features, especially HRA measures, as input is anticipated to enhance the efficacy of depression assessment and be utilized in clinical practice for diagnostic support.

From a clinical perspective, reductions in vagal activity have been verified, but the exploration of the impact of antidepressant treatment on HRV measures is demanded to validate the capacity of HRV as a psychophysiological biomarker for prognosis and prediction of therapy response in depression. Moreover, as understanding of the pathogenesis of depression deepens, the therapy affecting autonomic activity may become an option for addressing depression among adolescents.

Conclusion

Adolescents with MDD suffered a considerable decrease in vagal tone, along with reductions in time-domain and frequency-domain HRV measures and a heavy loss of short-term HRA and HRA compensation, compared to healthy controls. In contrast to the medium to large effect sizes observed in traditional HRV indices and their high sensitivity to the timing of data collection, nonlinear HRA features showed extremely large effect sizes in discriminating MDD with stable performance, and they also had a significant correlation with the severity of depression. The features focusing on the directionality of heart rate variations may provide further information on cardiac autonomic activity associated with depression. These findings contribute to better assessing the usefulness of HRV in adolescent depression.

Abbreviations

BMI	Body mass index
$C1_d$	Contributions of heart rate decelerations to short-term heart rate variability
$C2_d$	Contributions of heart rate decelerations to long-term heart rate variability
CI	Confidence intervals
ECG	Electrocardiogram
HDRS	Hamilton Depression Rating Scale
HF	High-frequency power
HRA	Heart rate asymmetry
HRV	Heart rate variability
LF/LF	Ratio of low frequency to high frequency
LF	Low-frequency power
MDD	Major depressive disorder
PNN50	Percentage of the number of successive heartbeats differing > 50 ms
PSQI	The Pittsburgh Sleep Quality Index
RMSSD	Root mean square of successive differences
SDNN	Standard deviation of RR intervals
TP	Total power

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Author contributions

Hang Chen, Zhenghe Yu, and Shulin Chen conceived and designed the study; Wanlin Chen and Haisi Chen interviewed participants and collected the data; Wanlin Chen, Wenchen Jiang, Cheng Chen, Moya Xu, and Haoxuan Ruan analyzed the data; Wanlin Chen, Haisi Chen, and Wenchen Jiang wrote the paper. All authors contributed to and have approved the final manuscript.

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Data availability

The datasets used and analyzed during the current study are available from the corresponding author (Shulin Chen) on reasonable request.

Declarations

Ethics approval and consent to participate

This study has been approved by Hangzhou Seventh People's Hospital Ethics Committee (No. 2024033). We confirmed that written informed consent was obtained from all participants and their parents. All methods in this study were performed by the guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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